REMARKS

In response to the above Office Action, claim 1 has been amended to include the subject matter of claim 6 which has been cancelled. Claim 7 has also been amended to now depend from claim 1. The claims now remaining in the case are claims 1-4, 7, 11-16 ad 19-22.

The present invention as defined in amended claim 1 relates to a method for the preparation of microspheres, which comprises the following circulation steps:

(a) emulsifying a medicament-containing polymer solution containing a medicament, a biocompatible and biodegradable hardly-water-soluble polymer and a water-immiscible organic solvent having a boiling point lower than that of water into an aqueous solution in an emulsifying device to form an emulsion wherein said medicament-containing polymer solution is dispersed in the aqueous solution;

(b) transferring the obtained emulsion into a microsphere storage tank;

(c) introducing a part of the emulsion from the microsphere storage tank into a cross flow filter;

(d-1)-i) returning a liquid passing over the cross flow filter to the microsphere storage tank;

(d-1)-ii) recycling a filtrate filtered from the cross flow filter as an aqueous solution for step (a), repeating steps (a) to (d-1), and evaporating said water-immiscible organic solvent with a hollow fiber membrane module located in the microsphere storage tank during this circulation process; and

(e) collecting microspheres in the microsphere storage tank after step (d-1) is completed.

According to this circulation method for the preparation of microspheres, the aqueous solution is effectively separated from the emulsion prepared in the emulsifying device and transferred into the microsphere storage tank with the cross flow filter, and during the circulation, the separated aqueous solution is utilized repeatedly for emulsification and the organic solvent is evaporated off in the microsphere storage tank. This method permits the apparatus used to prepare the microspheres to be considerably downsized and the production of the microspheres done effectively.

Moreover, according to the present method, even when a large amount of microspheres are to be produced, the emulsifying scale can be small. Hence, homogeneous emulsification can be easily done resulting in microspheres of high quality. Moreover, the production of the microspheres can be readily controlled by varying the emulsifying frequency.

In addition, the use of a hollow fiber membrane module to evaporate off the water-immiscible organic solvent in step (d-1)-ii) in the microsphere storage tank, allows for rapid evaporation of the water-immiscible organic solvent. Hence, this results in an increase in the efficiency of operating the process. See page 22, lines 19-21 and page 26, line 29 to page 27, line 19. See also Examples 1-3 beginning on page 38, where a hollow fiber membrane module is used in the process to improve the solvent removal efficiency.

In the Office Action the Examiner continued to reject the claims, including claim 6, under 35 U.S.C. §103(a) for being obvious over Suzuki in view of Lenk.

Suzuki, which belongs to the same assignee as the present invention, relates to a process for the preparation of microspheres from an emulsion in a vessel, wherein an

organic phase containing an organic solvent having a boiling point lower than that of water and a hardly-water-soluble polymer is emulsified in an aqueous phase. As exemplified in FIG. 1 of Suzuki, the process includes filtering the emulsion in the vessel (a^1) with a filter (e^1) and passing of the filtrate to a gas separation membrane module (b^1) to evaporate off the organic solvent.

More specifically, in this embodiment, identified as the Circulation Type of method and discussed beginning in paragraph [0114], a portion of the aqueous phase of the emulsion as a portion of the emulsion in the vessel is circulated to the gas separation membrane by the pump (c^1) and the taking of this portion is carried out by passing the emulsion through the filter. Thus the purpose of the filter is to filter out an aqueous phase as a filtrate for passage to the gas separation membrane where the organic solvent is evaporated off. The aqueous phase is thereafter returned to the vessel via line (g').

However, the filter used in Suzuki is a stainless mesh, glass or ceramic filter [0118] and is not a cross flow filter as claimed. Moreover, the gas separation membrane to which the portion of the aqueous phase of the emulsion as the filtrate of the filter is passed is located outside of the vessel. See FIG. 1.

The Examiner acknowledges at page 3, paragraph 9 of the Office Action these deficiencies in Suzuki where it is noted that Suzuki fails to disclose 1) a cross flow filter wherein the filtrate is recycled into the emulsifying apparatus and 2) evaporation of the organic solvent with a gas separation membrane located inside the vessel.

With respect to 1), the Examiner refers to Lenk. As pointed out in the Reply filed September 12, 2007, Lenk is merely concerned with the separation of particles such as

liposomes and lipid particles according to particle size using a cross flow filter. See Lenk col. 1, lines 14-16. This represented an alleged improvement over the use of traditional "dead-end" filtration processes for the separation of such particles.

Nevertheless, the Examiner argues that it would have been obvious to use a cross flow filter in the process of FIG. 1 of Suzuki because of the advantages noted by Lenk of the use of such type of filtration in place of traditional filtration such as described in Suzuki. See paragraph 10 of the Office Action.

With respect to 2), the Examiner points to another embodiment disclosed in Suzuki and exemplified in FIG. 2 where the gas separation membrane is located inside the vessel. In this embodiment, identified as the "Immersing Type" of method for evaporation of the organic solvent and discussed beginning in paragraph [0128], the gas separation membrane is a tubular gas separation membrane and in the form of bundles of plural gas membrane which form hollow fibers . . . and the bundle is immersed in the emulsion and a gas is passed into the inner side of the tubular gas separation membrane. (See Suzuki, paragraph [0129]. See also Examples 6, 8, 9, 10, 11, 12, and 13, where the microspheres are prepared by this immersing type of separation method, and the emulsion is located outside of the hollow fiber separation membrane. This allegedly avoids any problem of clogging of the hollow fiber gas separation membrane.

Significantly, no filter is used in this process. Nevertheless, the Examiner believes in view of this teaching, that it would have been obvious to locate the gas separation membrane of FIG. 1 "inside the vessel" in view of the teachings of FIG. 2. See paragraph 11 of the Office Action.

In essence then the Examiner is arguing that it would have been obvious to 1) replace the filter (e') in FIG. 1 of Suzuki with the cross flow filter of Lenk and 2) replace the gas separation membrane module (b^1) located outside the vessel (a^1) with a gas separation membrane located "inside the vessel" in view of FIG. 2 of Suzuki. See page 4, lines 7-9 of the Office Action, where the Examiner argues that "it would have been obvious . . . to evaporate the organic solvent inside the vessel in the process taught by the combination of Suzuki and Lenk" (Emphasis added).

However, not only would the combination of 1) and 2) be illogical, but it would probably render the process resulting from the modified apparatus inoperable or at least not satisfactory for its intended purpose. The Examiner cannot take these two modifications of the apparatus of FIG. 1 of Suzuki and the process steps resulting from them separately, ignoring the impact one might have on the other. To use them as a basis for rejection of the claims, the modified apparatus and resulting process steps must be considered as a whole.

Moreover, as will be discussed in more detail below, even the combination proposed by the Examiner still does not meet all of Applicants' claimed steps in the process.

First of all, assuming, for the sake of argument, it was obvious to substitute a cross flow filter for the ceramic filter (e') in the device of Suzuki in FIG. 1 in view of Lenk and even to return the liquid passing over the filter back to the vessel, the purpose of the filter of Suzuki is to provide a filtrate for passage to a gas separation membrane. Yet the Examiner has now placed this membrane inside the vessel. Where then does this filtrate go? The only way to get it to the gas separation membrane where it is to go

is to return it also to the vessel, but then why filter it in the first place if both what passes over the filter and what goes through it go back to the vessel? The process would then really be no different than the process that occurs in the device of FIG. 2 of Suzuki because the "cross flow filter" would have no purpose.

The Examiner argues on page 6, lines 1-2 of the Office Action "that the combination of two methods . . . to form a third method useful for the same purpose is prima facie obvious" (Emphasis added). This is correct, but it is not if it is not useful for the same purpose. As pointed out above, the proposed combination does not, in fact, form a third method, but one at best no different than before.

In summary, it might be obvious to use a cross flow filter in place of the filter (e^1) of Suzuki in view of Lenk returning what passes over the filter back to the vessel (a^1) and the filtrate to the gas separation membrane module (b^1) located outside the vessel, but it would make no sense to use one when the gas separation membrane module is located inside the vessel.

As noted in M.P.E.P. §2143.01, if the prior art being modified is rendered unsatisfactory for its intended purpose, then there can be no suggestion or motivation to make the proposed modification.

Secondly, in making the rejection, the Examiner has ignored the step in step (d-1)-ii) of claim 1 of "recycling a filtrate filtered from the cross flow filter as an aqueous solution for step (a)" and its relation to the other claimed steps. In step (a) the emulsion is first formed in "an emulsifying device" (1) which is then transferred in step (b) to the microsphere storage tank (2), which the Examiner equates to Suzuki's vessel (a^1). No such emulsifying step separate from the vessel is taught in Suzuki, nor is there the

slightest suggestion in Suzuki or Lenk of "recycling the filtrate" from the cross flow filter to it, even if Suzuki contained a cross flow filter. In Suzuki, the filtration is done for the organic removal step, whereas in the claimed invention the filtration is done for the emulsifying step. This is a significant difference over Suzuki whether combined with Lenk or not.

Consequently, it is submitted that the Examiner has not clearly articulated all of the reasons why the claimed invention would be obvious as required by M.P.E.P. §§2142 and 2143 to establish a prima facie case of obviousness, because she has not articulated where the prior art teaches or how it could be modified to show recycling of the filtrate of the cross flow filter to an emulsifying device that is separate from and outside of the microsphere storage tank where the gas separation membrane is located. The Examiner argues that since Suzuki returns the filtrate of the filter back to the vessel (a^1) where the emulsion is being formed, that this meets Applicants' claim limitation. See page 6, paragraph 18. However, the Examiner ignores the fact that this is also the microstorage tank and that she has already located the gas separation membrane in this vessel to meet Applicants' claims. The claims do not return the filtrate to such a vessel, but rather to an emulsifying device separate from it where the emulsion is formed, because in the claimed process, the aqueous emulsion formed in the emulsifying device is "transferred" in step (b) to the microsphere storage tank/vessel. The Examiner has not shown where this step is shown in the references or how they could be modified to include it.

In addition to the fact the Examiner has not shown how Applicants' claimed process could result from the proposed modification of the cited references, many

advantages result from Applicants' claimed circulation process. These include the ability to downsize the apparatus to be used without sacrificing production scale, efficiency, quality or control.

With respect to downsizing of the apparatus, it is disclosed in the specification, for example, at page 20, lines 10 to 13, that for preparing microspheres from an emulsion, the volume of the aqueous solution in the emulsion is in the range of from 10 to 300 times the volume of the medicament-containing polymer solution, and the emulsion produced is mostly (in volume) composed of the aqueous solution.

Assuming that the medicament-containing polymer solution is used in an amount of 100 L and the aqueous solution is in an amount of ten times (1000 L) of the volume of the medicament-containing polymer solution (that is, the minimum amount of aqueous solution is used), if the microspheres are prepared at one time as in either methods of Suzuki by using the above-mentioned amounts of solutions, the emulsion thus prepared will have a volume of about 1100 L. Hence, the microsphere storage tank must have a size able to contain such a large amount of emulsion.

On the other hand, when the microspheres are prepared by the method of the present invention by using the solutions in the same amounts as assumed above, the emulsion can be prepared in portions by using a cross flow filter, for example by using the medicament-containing polymer solution in an amount of 10L and the aqueous solution in an amount of 100 L, followed by transferring the resulting emulsion to the microsphere storage tank, where the organic solvent is evaporated off. In parallel with the above procedure, the emulsion is filtered with a cross flow filter, and the filtrate (i.e., an aqueous solution) thus separated is repeatedly used for emulsification of the

medicament-containing polymer solution in the emulsifying device. The procedure is repeated many times to complete the preparation of the desired microspheres. In this method of the present invention, the microsphere storage tank requires merely a volume of about 110 L.

Thus, even when a medicament-containing polymer solution of the above amount is used, the volume of the microsphere storage tank need only be about one tenth the size in comparison with that to be used in the methods of Suzuki.

With respect to the efficiency of the claimed process, if the method of Suzuki is carried out using a microsphere storage tank having a small size, it would have to be done repeatedly by repeating the emulsification step, the evaporation of the organic solvent, the recovery of the produced microspheres, and the like, in order to prepare a large amount of microspheres. On the other hand, according to the claimed method of the present invention, because of the evaporation of the organic solvent with a hollow fiber module located within the microsphere storage tank, in parallel with the steps of filtration of the emulsion with a cross flow filter and of use of the filtrate for emulsification, a large amount of microspheres can be prepared with high efficiency.

Moreover, in order to remove/evaporate the organic solvent from the emulsion in an amount corresponding to the amount of microspheres to be produced, a large scale of apparatus is required in the method of Suzuki. On the contrary, according to the method of the present invention, the same scale of apparatus can be used regardless of the amount of the microspheres to be produced because the emulsification is repeatedly done by using as the aqueous solution the filtrate obtained by filtering the emulsion with the cross flow filter. In other words whether microspheres of 1 kg are

produced or of 10 kg are produced, the same size of apparatus can be used. Thus, the scale of production of the microspheres can be readily controlled.

Applicants would also like to point out that the ratio of the amount (volume) of the aqueous solution to the amount (volume) of the medicament-containing polymer solution is very important in the preparation of microspheres because it affects the quality of the produced microspheres. Generally speaking, the smaller the volume ratio of the aqueous solution, the lowering of the solidification speed of the oil drops contained in the emulsion, and hence the lowering of the contents of the medicament in the microspheres.

Therefore, there has been concern about a lowering of the quality of the microspheres if the filtrate of the emulsion is used for emulsification, because the filtrate contains residual water-immiscible organic solvent which may cause a lowering of the solidification speed of the oil drops of the emulsion. Contrary to this concern, however, according to the method of the present invention, it has surprisingly been found that there is not such a problem, because the organic solvent is effectively removed by the hollow fiber module located in the microsphere storage tank and a lowering of the quality of product (lowering of content of medicament) is inhibited. For example, the products in Examples 1 to 3 of the application have a content of the medicament (i.e., leuprolide acetate) of 9.13%, 8.87% and 10.05%, respectively. See page 41, lines 22-23; page 42, lines 19-22; and page 45, lines 4-7 of the specification. On the other hand, in Example 13 of Suzuki, the content of the same medicament was only 7.5%. See paragraph [0225].

In summary, while it might have been obvious to use the cross flow filter of Lenk in Suzuki, it would not be used for the same purpose or in the same manner as claimed. This is apparent from the Examiner's failure to recognize the illogical result of her attempt to combine Suzuki and Lenk to form "a third method" and her failure to show the claimed step of using the filtrate from the cross flow filter in an emulsifying step and not in an organic removal step as in Suzuki.

It is submitted, therefore, that neither claim 1 nor claims 2-4, 7, 11-16, and 19-22 dependent therefrom are obvious over Suzuki in view of Lenk. Their withdrawal as a ground of rejection of the claims under §103(a) is, therefore, requested.

It is believed claims 1-4, 7, 11-16, and 19-22 are in condition for allowance.

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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